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Renoprotection with and without blood pressure reduction

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Background. AT1-receptor blockade dose dependently lowers blood pressure (BP) and albuminuria. Reduction of BP and albuminuria are independent treatment targets for renoprotection, but whether this requires similar dose titration is unknown.

Methods. We tested this in two studies designed to find the optimal antialbuminuric dose of losartan in type 1 diabetic (DM, $N = 50$) and nondiabetic renal patients (ND, $N = 12$). After baseline, treatment followed with losartan 50, 100, and 150 mg/day, each dose for eight (DM) or six weeks (ND). At the end of each period, albuminuria (24-hour samples) and mean arterial pressure (MAP) were measured. Patients were divided into "good" and "poor" BP responders (BP+, BP−) according to BP response above or below group median.

Results. Baseline MAP in the BP− groups was 102 (97, 104) mm Hg in DM (median, 95% CI) and 91 (80, 108) mm Hg in ND. The top of the dose response for BP (obtained at losartan 100 mg) in the BP− groups was −2 (−4, 3) mm Hg in DM and –1 (−6, 2) mm Hg in ND, versus −15 (−18, −12) mm Hg and −16 (−26, −18) mm Hg in BP+ groups (both $P < 0.05$). Albuminuria was reduced dose dependently both in BP− and BP+: with 100 mg, the reduction in albuminuria in DM BP− was −32% (−49, 13) versus −45% (−60, −38) in DM BP+ and −45% (−70,−7) versus –25% (−58, −6) in ND BP− and BP+ (all $P > 0.05$). Moreover, in patients in whom BP fell below the recommended treatment target of 130/80 mm Hg (13 in DM and 10 in ND), albuminuria was progressively reduced, with further increasing the dose of losartan in most patients.

Conclusion. Absence of BP response to losartan does not preclude a reduction in albuminuria, and optimal reduction of albuminuria may require titration beyond the predefined BP target.

Raised blood pressure [1] and proteinuria [2] are modifiable risk factors in progressive renal function loss in diabetic, as well as nondiabetic, renal disease. It is well recognized that lowering blood pressure with antihypertensive treatment slows progressive renal function loss [3]. Additional lowering of proteinuria by specific antihypertensive treatment regimens like renin-angiotensin system (RAS) blockade is associated with a slower decline of renal function compared to other treatment groups with similar blood pressure [4, 5]. Thus, it has been argued that reduction of blood pressure and proteinuria should be independent treatment goals [6].

RAS blockade with ACE inhibitors or angiotensin II, type 1 receptor blockers (ARB) is so far the most effective pharmacologic tool for long-term renoprotection. These agents have the advantage of reducing proteinuria more effectively than other antihypertensives do [7].

As these drugs were originally introduced as antihypertensives, it is still common practice to titrate the dose of these agents to reach a prespecified blood pressure target. However, we [8, 9] and others [10, 11] have shown that proteinuria, too, is sensitive to the dose of these drugs, and the optimal dose for proteinuria may not always be similar to that for blood pressure. Importantly, there is considerable interindividual variability, both in the antihypertensive response [12] and the antiproteinuric response [13] to RAS blockade. Presumably, the antiproteinuric response is, to a certain extent, dependent from the effect on systemic blood pressure. This does not automatically imply, however, that the observed interpatient variability in the blood pressure and antiproteinuric response are concordant. In other words, whether a good—or poor—blood pressure response is always accompanied by a respectively good—or poor—response for proteinuria in a given patient is unknown so far. In the present analyses, therefore, we tested first whether dose-dependent reduction of proteinuria is concordant with the blood pressure dose-response to RAS blockade with the ARB losartan. Second, we tested whether achievement of a predefined blood pressure target (i.e., the current clinical practice), results in the optimal reduction of proteinuria.

METHODS

Patients and methods

Individual patient data were used from two recent studies that were designed to find the optimal dose of losartan for reduction of proteinuria [8, 9]. The study designs and inclusion criteria of the original investigations have

Key words: albuminuria, blood pressure response, diabetes mellitus, losartan, proteinuria, renoprotection.

Table 1. Patient characteristics in subgroups according to break-up for blood pressure response

	Diabetic patients		Nondiabetic patients	
	Good BP responders ($N = 21$)	Poor BP Responders ($N = 22$)	Good BP responders ($N = 6$)	Poor BP responders ($N = 6$)
Age *years*	43 (41, 52)	43 (40, 50)	45 (39, 51)	53 (43, 59)
Male/female	17/4	11/11	3/3	4/2
Albuminuria *g/day*	1.3 (1.0, 2.3)	1.2 (0.9, 1.7)	4.5 (3.0, 6.9)	2.4 (1.7, 3.8)[a]
Systolic BP *mm Hg*	161 (152, 169)	150 (143, 155)[a]	142 (126, 163)	127 (113, 152)
Diastolic BP *mm Hg*	84 (80, 88)	79 (73, 82)[a]	82 (74, 96)	74 (63, 87)
MAP *mm Hg*	108 (104, 113)	102 (97, 104)[a]	102 (91, 118)	91 (80, 108)
GFR	87 (74, 102)	96 (84, 102)	82 (46, 100)	85 (61, 104)
Na excretion *mmol/day*	171 (151, 193)	138 (129, 172)	115 (83, 146)	120 (80, 159)

[a] $P < 0.05$ vs. good BP responders. No comparisons were made between diabetic and nondiabetic patients.

been shown extensively in the original papers. In short, the first was a study in 50 patients with type 1 diabetes mellitus and nephropathy (DM), and the second study was performed in 12 nondiabetic patients (ND) with various glomerular disorders and proteinuria. Only patients with diastolic blood pressure between 80 and 110 mm Hg were included. Two nondiabetic patients that fulfilled the same protocol were included in the present analyses. The protocols were largely similar, and started with a washout period of four to six weeks before enrollment in the study (withdrawal of all antihypertensives). Then, treatment with losartan was followed according to fixed dosing steps. All patients were treated with 50, 100, and 150 mg/day losartan, and each dose was used for eight (DM) or six weeks (ND). Data were collected at the end of each period. Blood pressure was measured by 24-hour ambulatory measurements (DM), or with a Dinamap device after 15 minutes of supine rest (ND). Renal function was assessed by [51Cr] EDTA plasma clearance (DM) or by calculating creatinine clearance from 24-hour urine (ND). Albuminuria was measured from at least two 24-hour urine collections (Cobas Mira Plus; Roche, Montclair, NJ, USA). In order to allow comparison of baseline albuminuria, random urine samples were exchanged between both laboratories for measurement of albuminuria, and a conversion factor was established, yielding a correlation with $R^2 = 0.98$. Albuminuria in the nondiabetic patients was then calculated by this conversion factor. In both studies, the use of antihypertensives, other than the study drug, was not allowed.

The responses of blood pressure and albuminuria are expressed as percentage change from baseline (median and 95%CI). Comparison of the antialbuminuric response between groups was performed using Mann-Whitney *U* test, and comparisons within groups were performed using Wilcoxon signed rank test. Differences were considered significant if $P < 5\%$.

Analysis 1: Antialbuminuric dose response in the "poor" and "good" blood pressure responders

First, we questioned whether interindividual variability in the dose response of blood pressure and albuminuria were concordant. To test this, groups of "poor" and "good" BP responders were defined. Patients from both studies were separated into two groups according to the blood pressure response by calculating the average response to the three doses used in each patient. Patients were then, according to the group median, attributed to the group of poor BP responders or good BP responders. Then, the effect on albuminuria of increasing doses of losartan was tested in good and poor responders. Because the protocols were not entirely similar, the data on the diabetic and nondiabetic patients were not pooled and are presented separately.

Analysis 2: Step-up dosing beyond the blood pressure target: effect on albuminuria

The second question was whether the use of predefined blood pressure criteria in treating renal patients results in optimal reduction of proteinuria. To answer this, we established at each dose that patients were below the predefined target blood pressure, and then evaluated whether further increases of the losartan dose led to a further decrease of albuminuria. The target used is the target for type 1 diabetic patients with renal involvement as formulated by the American Diabetes Federation (i.e., a systolic BP $\leq$130 mm Hg and a diastolic BP $\leq$80 mm Hg).

RESULTS

Antialbuminuric dose response in the "poor" and "good" blood pressure responders

From the original study in diabetic patients, 43 patients with complete blood pressure registrations were eligible for the present analysis, while all 12 nondiabetic patients were included. The 7 diabetic patients not included in the present analysis had baseline GFR 88 mL/min and albuminuria 1.3 g/day (range: 0.3, 4.0 g/day) and the reduction of albuminuria was –38% (range: –91, 16%). These characteristics were not different from those of the included diabetic patients, shown in Table 1. The patients from both populations were middle-aged, and had mild to moderately impaired renal function. In nondiabetic patients, baseline albuminuria was higher than in

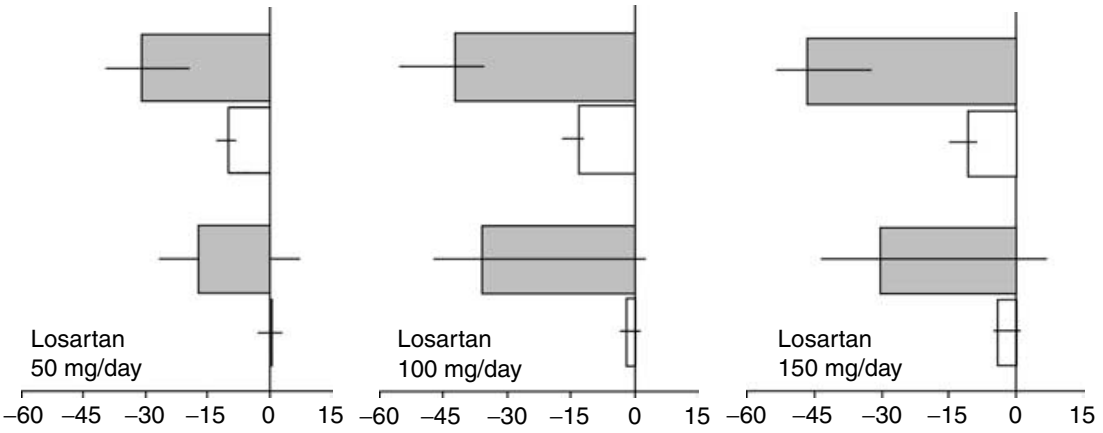

Fig. 1. The antialbuminuric response (gray bars) and blood pressure response (white bars) at each dosing step, represented as% Δ from baseline, in the total population of diabetic and nondiabetic patients. The upper part of the graph shows the subgroup of "good BP responders," the lower part of the graph shows the subgroup of "poor BP responders" (i.e., a BP response above or below the median of the total population, respectively).

the diabetic patients. The good BP responders of both populations tended to have a higher baseline blood pressure compared to the poor blood pressure responders, but this difference reached statistical significance only in the diabetic patients.

The responses of proteinuria and blood pressure are depicted in Figure 1. In the poor BP responders, that is, a BP response below the median, the blood pressure response was virtually absent across all three dosing steps. As expected, a clear-cut blood pressure response was observed in the group designated good BP responders, confirming that the break-up by the median indeed effectively identified "poor" and "good" responders.

Interestingly, albuminuria was reduced considerably and dose dependently in the "poor" BP responders: the antialbuminuric response by the 100 mg dose was higher than by the 50 mg dose (both 100 mg vs. 50 mg dose, $P < 0.01$), and the 150 mg dose had no additional benefit at group level.

The antialbuminuric response of poor BP responders is given separately for the diabetic and nondiabetic patients in Table 2. It shows that albuminuria was reduced in both subsets of patients without a blood pressure response. Possibly due to the size of the subgroups, both in the diabetic and nondiabetic patients, there was no clear difference between the antialbuminuric efficacy in the poor BP responders versus the good BP responders.

Table 2. Antialbuminuric response in diabetic and nondiabetic poor BP responders

	Losartan dose *mg/day*		
	50	100	150
Diabetic	−15% (−28, 13)	−32% (−49, 13)[a]	−30 (−47, 17)[a]
Nondiabetic	−21% (−51, 12)	−45% (−70, −7)[a]	−32% (−61, −1)[a]

[a] $P < 0.05$ vs. baseline.

Step-up dosing beyond the blood pressure target: effect on albuminuria

In the diabetic patients, only 13 out of 43 reached the blood pressure target of 130/80 mm Hg during the protocol. Ten out of the 12 nondiabetic patients reached the blood pressure target. The antialbuminuric responses of the patients that reached the target blood pressure of 130/80 mm Hg are shown in Figure 2 (diabetic patients) and Figure 3 (nondiabetic patients). The target was reached without antihypertensive medication in two (DM) and five (ND) patients. In the patients who were on target without therapy (Figs. 2A and 3A), a considerable decrease in albuminuria was observed with increasing the losartan dose. In the patients that reached the target at the 50 mg dose of losartan (Figs. 2B and 3B), increasing the dose resulted in further reduction of albuminuria in all but one patient. In patients that reached target blood pressure at the 100 mg dose (Figs. 2C and 3C), additional antialbuminuric benefit was observed in the majority (i.e., six out of nine patients), by increasing the dose to 150 mg. In summary, there was a general tendency that increasing losartan beyond the dose at which target blood pressure was reached resulted in additional reduction of albuminuria.

In the patients that did not reach the blood pressure target at the consecutive dosing steps (30/43 diabetics and 2/12 nondiabetics), this did not preclude a significant reduction of albuminuria. The median fall in albuminuria in the diabetic patients was −22% (−29; −9), −34% (−43; −20), and −38% (−42; 5) with losartan 50, 100, and 150 mg/day, respectively (all doses: $P < 0.05$ vs. baseline, and 50 vs. 100 mg dose: $P < 0.05$).

DISCUSSION

For long-term renoprotection, antihypertensive treatment with RAS blockade has the major advantage of its

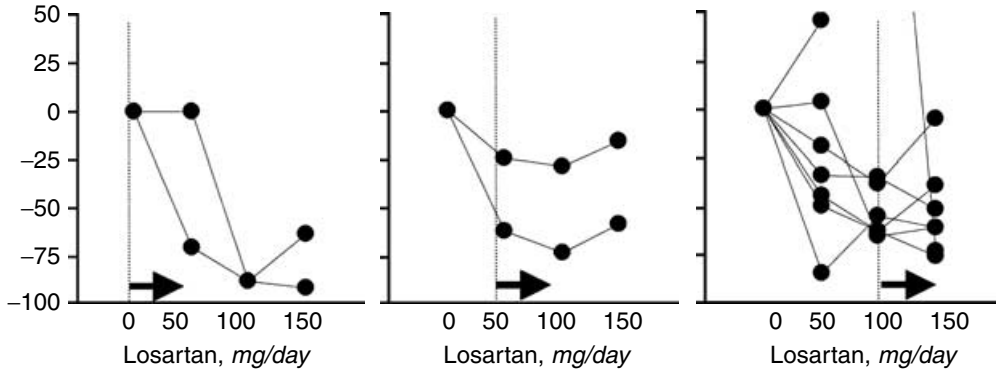

Fig. 2. The effect on albuminuria (%Δ from baseline) of step-wise increasing the dose of losartan in individual diabetic patients who reached the target BP of 130/80 mm Hg. The vertical dotted lines indicate the dose at which target BP has been reached. (*A*) Patients who reached target BP at baseline. (*B*) Patients who reached target BP at the 50 mg dose. (*C*) Patients who reached target BP at the 100 mg dose.

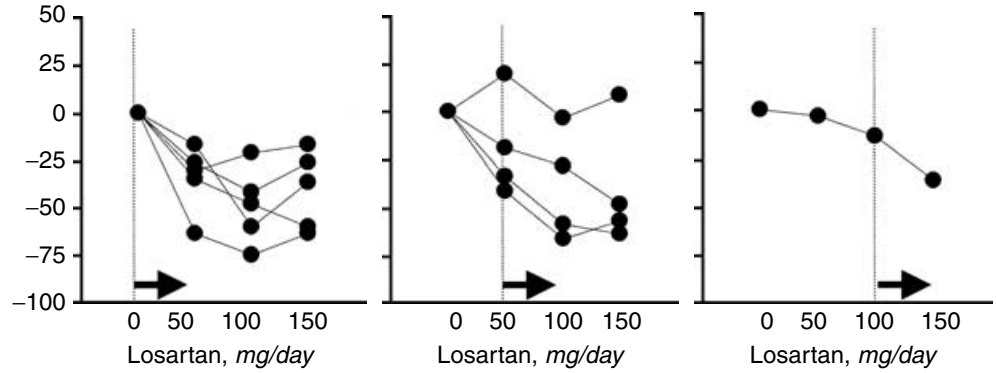

Fig. 3. The effect on albuminuria (%Δ from baseline) of step-wise increasing the dose of losartan in individual nondiabetic patients who reached the target BP of 130/80 mm Hg. The vertical dotted lines indicate the dose at which target BP has been reached. (*A*) Patients who reached target BP at baseline. (*B*) Patients who reached target BP at the 50 mg dose. (*C*) Patients who reached target BP at the 100 mg dose.

specific antiproteinuric effect. Blood pressure and proteinuria are both considered independent treatment targets, but it is currently unknown how to titrate RAS blockade to bend the curve of renal function loss.

One issue of importance in this respect, addressed in the present study, is whether the blood pressure lowering effect and antiproteinuric effect run in parallel in individual patients. This study shows that the opposite is true, that is, a clinically important antiproteinuric dose response can be observed in patients that are basically nonresponsive with respect to systemic blood pressure, even at high doses of the ARB losartan. Moreover, in the subset of patients who had already reached the desired blood pressure, a further increment in the dose resulted in a progressive fall in proteinuria in most subjects.

It must be stressed that secondary analyses like ours must be considered with caution and need to be confirmed in prospective follow-up studies. Nevertheless, the findings on the effect of the ARB on blood pressure response and albuminuria were consistent between the larger diabetic group and the smaller nondiabetic group. It also must be stressed that the response of albuminuria and blood pressure to ARB was measured at three consecutive doses. Thus, absent or poor blood pressure response is unlikely to have occurred because of random fluctuations. Because the data were obtained in two separate populations with different renal diseases, this indicates that our findings are not limited to a single center or method of data collection (e.g., measurement of blood pressure).

Previous studies have shown that, with low doses, the antiproteinuric effect obtained with RAS blockade is more pronounced than would be expected merely from the effect on systemic blood pressure [7, 14, 15]. By showing that patients who are apparently insensitive with respect to blood pressure have antiproteinuric benefit from dose titration with RAS blockade, the present report extends the previous findings usually obtained with low doses of RAS blockers. It thus provides practical relevance to the increasingly advocated view to consider proteinuria, in addition to blood pressure, as an independent target for long-term renoprotection [6, 16–18]: because of the lack of concordance between the responses of both parameters, optimal reduction of proteinuria is unlikely

to be reached with the current practice of aiming at predefined levels of blood pressure.

It could be argued that, in order to prevent the possibility of carryover, the doses should have been given in random order. However, previous studies have shown that the antiproteinuric effect of losartan reaches its maxmimum after three to four weeks of treatment [abstract; Preti et al, *Am J Hypertens* 11:112A, 1998]. Also, a double-blind cross-over study with losartan 50 and 100 mg in randomized order showed that the magnitude of the reduction of blood pressure and albuminuria did not depend on the order of treatment [19].

Interindividual variability in the antiproteinuric response to RAAS blockade is increasingly recognized as an issue, important for improvement of long-term renoprotective therapy [20, 21], recently reviewed in [22]. The present results do not exclude the possibility that an individual's blood pressure response contributes to this variability. Nevertheless, it is apparent that other factors must be involved that play a more critical role in this respect.

It is beyond doubt that blood pressure should be controlled tightly to slow progressive loss of renal function, both in diabetic and nondiabetic nephropathy [3, 23]. In addition to blood pressure, proteinuria is the strongest independent predictor of end-stage renal disease [24], and regimens reducing proteinuria slow the deterioration of renal function, independent of the blood pressure effect [23, 25, 26]. Although all these data indicate that proteinuria should probably be lowered as much as possible, until now, no clinical trials addressed whether a regimen pursuing maximal reduction of proteinuria as a treatment goal allows further improvement of renoprotective efficacy.

In clinical practice, blood pressure targets are hard to reach, especially in patients with diabetes. In line with this, in the present study with a fixed step-up dose schedule, 30 out of 43 diabetic patients and 2 out of 12 patients did not reach the target blood pressure of 130/80 mm Hg. These patients would, thus, require up-titration, and likely add-on therapy, for the sake of blood pressure. Nevertheless, also in these patients a significant fall in albuminuria was observed.

CONCLUSION

This study with the ARB losartan shows that a fall in blood pressure is not a prerequisite for a dose-dependent reduction of proteinuria, both in diabetic and nondiabetic renal disease. This supports the idea that renoprotective treatment should be titrated according to both blood pressure as well as proteinuria. Large randomized clinical trials will be necessary to study the long-term renal prognosis of lower proteinuria levels obtained with such a strategy.

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